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(54) PREPARATION OF DIARYL ETHERS AND THIOETHERS

(71) We COALITE AND CHEMICAL PRODUCTS LIMITED, a British Company, of Buttermilk Lane, Bolsover, near Chesterfield, Derbyshire, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to a process for the preparation of diaryl ethers and thioethers or sulphides.

It is common practice to form diaryl ethers by reacting at elevated temperature a potassium phenoxide with a nucleophilically activated aryl halide, the reaction being carried out dry or in the presence of an excess of the phenol and copper or a copper compound. The reaction temperature is somewhat high and side reactions occur with the production of a dark, discoloured product. Further, it is difficult to separate the potassium halide from the reaction product.

Patent No. 1,016,648 claims 2,4,6-trichloro-4'-nitrodiphenyl ether and 2-methyl-4,6-dichloro-4'-nitrophenyl ether and a method for their preparation by reacting p-nitrochlorobenzene with an alkali metal 2,4,6-trichlorophenolate or an alkali metal 2-methyl-4,6-dichlorophenolate. In the Examples in that Patent, the phenate is either produced from the phenol and potassium hydroxide and is thus used in the reaction as the potassium salt or is produced from a mixture of sodium and potassium hydroxides and is thus used in the reaction as a mixture of the sodium and potassium salts. In two of the three Examples which are given, the reaction is carried out at 200°C for 20 hours with yields of 72.8% and 72.4%. In the third Example, the reaction is carried out at 160°C for 10 hours with a yield of 71.3%.

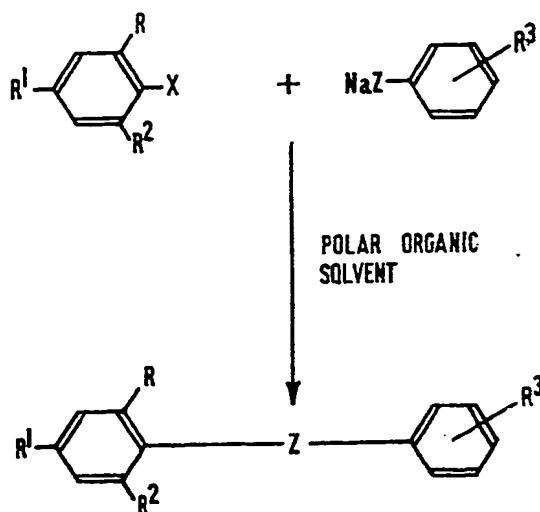
It is an object of the invention to provide a process for the production of diaryl ethers or sulphides in which one or more of the disadvantages of the prior art process are mitigated.

According to the invention, a diaryl ether or thioether is produced by reacting a sodium aryl compound $ArZNa$ with an aryl compound $Ar'X$ in a polar organic solvent, in which Ar and Ar' are aryl groups which may be the same or different, Z is $-O-$ or $-S-$ and X is a nuclear, replaceable halogen or pseudohalogen.

X is preferably chlorine. When X denotes a pseudohalogen, it may be cyanide, cyanate, isocyanate, thiocyanate or isothiocyanate.

The aryl compound $Ar'X$ preferably contains at least one further nuclear substituent which is an electron-withdrawing group to render the substituent X more labile and so facilitate its replacement in the reaction. The further nuclear substituent is suitably a nitro group but it may be any other electron-withdrawing group, for example, a carbonyl group. When the compound $Ar'X$ is a substituted benzene, the nitro or other electron-withdrawing group is preferably ortho or para to the substituent X .

The condensation may be represented thus—



in which at least one of R, R' and R² is an electron-withdrawing group and the other or others are hydrogen or substituents which do not unduly hinder or prevent the condensation, and R³ denotes one or more substituents which do not unduly hinder or prevent the condensation. Thus R and R', and R³ if present in the 2- and/or 6-position, should not be of such bulk or structure as to prevent the condensation from taking place.

The polar organic solvent may be an N-alkylated alkanolic acid amide, N,N-dimethylformamide being particularly suitable.

In one preferred method of carrying out the invention, the phenoxide or its sulphur analogues is prepared in situ by mixing a concentrated aqueous sodium hydroxide solution with a solution or suspension of the phenol or thiophenol in a liquid medium which forms an azeotrope with water. The sodium hydroxide and the phenol or thiophenol are advantageously used in substantially equimolar proportions. The liquid medium is suitably toluene but it will be understood that the toluene may be replaced with many other suitable azeotrope formers. The water, both that introduced and that evolved in the formation of the phenoxide or sulphide, is then removed by azeotropic distillation. The residual toluene or other liquid medium is then preferably removed as far as conveniently possible. The polar organic solvent and the aryl halide are added and the reaction mixture is maintained at a temperature which permits the condensation reaction to take place. The aryl halide is preferably added in an amount equimolar to the phenoxide or sulphide. The concentration of the reaction solution is conveniently between one and two molar but a higher concentration may be used. At the end of the reaction, the sodium halide is removed by filtration and the product may be worked up by distillation and crystallisation.

The optimum reaction temperature or temperature range for a particular reaction mixture may be readily determined by simple experiment. With an N-alkylated alkanolic acid amide, particularly dimethylformamide, as the polar organic solvent and monocyclic compounds as the two aryl reactants, a reaction temperature in the range 80—140°C is generally suitable, particularly in the production of the ethers, that is, when Z denotes O.

When the reaction is carried out at a temperature below 100°C, the inorganic salt, particularly sodium chloride, is deposited in a form which makes filtration difficult. It is therefore preferred that the reaction be effected at a temperature not below 100°C, for example a temperature in the range 100—130°C. When, however, the reaction has been carried out at a temperature below 100°C, the difficulty in filtering the inorganic salt can be overcome or mitigated by holding the reaction mixture for a short time at a temperature above 100°C, for example at a temperature in the range 110—130°C, particularly about 120°C, before filtration is effected.

In the production of the thioethers, the use of higher reaction temperatures is frequently advantageous, for example temperatures above 140°C and preferably temperatures in the range 140—200°C. With suitable polar organic solvents, for example

N-methylacetamide and dimethylformamide, the reaction can then be carried out under reflux at atmospheric pressure. It will be understood that the polar organic solvent may be other than an N-alkylated alkanolic acid amide. It may, for example, be dimethyl sulphoxide.

The process according to the invention, using the sodium ion instead of the more expensive potassium ion, enables the product to be produced in a single reaction vessel. The reaction may be effected at a moderate temperature and the sodium chloride or other halide can be removed from the product by simple filtration. The diaryl ether or sulphide may be obtained in good yield in a relatively short time at a moderate temperature. Furthermore, the diaryl ether or sulphide is obtained in a good state of purity and may be separated from the liquid reaction medium by simple procedures, whilst the reaction medium is readily recovered without undue loss.

The invention is illustrated in the following examples.

Example 1

4-nitro-4'-chlorodiphenyl ether

1 mole 4-chlorophenol was dissolved with agitation in approximately 1 litre pure toluene. 1 mole sodium hydroxide was added as a 70% w/v solution in water and the water which was added in the aqueous sodium hydroxide and that evolved in the reaction between the phenol and the sodium hydroxide, was removed by azeotropic distillation using a Dean and Stark apparatus. When the removal of water was complete, distillation was continued until approximately 900 ml of toluene had been removed. 1 litre of N,N'-dimethylformamide was then added with 1 mole 4-chloronitrobenzene. The temperature was raised to 120°C and maintained at that temperature for three hours. The reaction mixture was then cooled to about 100°C and filtered to remove salt. The filtrate was placed in a distillation apparatus and the solvent removed by distillation. The pressure was then gradually reduced to 4 Torr and the product distilled at 189°C. The yield of 4-nitro-4'-chlorodiphenyl ether was 240 grams (96% of theory).

Example 2

4,4'-dinitrodiphenyl ether

One mole of 4-nitrophenol was treated in an identical manner to the 4-chlorophenol in Example 1 up to and including the addition of the 1 mole of 4-chloronitrobenzene and the litre of N,N'-dimethylformamide. The toluene was removed from the reaction mixture by fractionation in a column of three theoretical plates. Distillation was then continued until a total of 700 mls dimethylformamide has collected. The reaction mixture was then cooled somewhat and filtered hot to remove salt. The hot liquor was then cooled and the crystallised product filtered off and dried. The yield of crystals was 215 grams (82% of theory).

A further 12 grams of 4,4'-dinitrodiphenyl ether was found upon analysis to be present in the mother liquors.

Example 3

2-nitro-4'-chlorodiphenyl ether

182.5 grams 4-chlorophenol were converted into the anhydrous sodium salt as described in Example 1. After removal of approximately 80% of the added toluene a mixture of 157.5 grams of 2-nitrochlorobenzene and one litre of dimethylformamide was added and a short fractionating column was fitted. Fractionation was continued until only pure dimethylformamide distilled. Distillation was continued until the temperature of the reaction mass reached 180°C. It was then cooled somewhat and poured into 4 litres of vigorously stirred water. After filtering and drying, a solid was obtained which weighed 248 grams and which was shown to contain 96% 2-nitro-4'-chlorodiphenyl ether.

Example 4

2,4-dinitrodiphenyl ether

Example 3 as repeated except that the phenol used was phenol itself and 202 grams of 2,4-dinitrochlorobenzene were used instead of the 2-chloronitrobenzene. 260 grams of solid were recovered and it contained 93% 2,4-dinitrodiphenyl ether.

Example 5

4-nitro-2',5'-dichlorodiphenyl ether

Example 3 was repeated but with the use of 163 grams of 2,5-dichlorophenol

instead of the 4-chlorophenol and 157.7 grams of 4-nitrochlorobenzene in place of the 2-nitrochlorobenzene.

Example 6

4-nitro-2'-methoxydiphenyl ether

5 Example 5 was repeated but using 124 grams guaiacol instead of the 2,5-dichlorophenol. The yield of solid product was 235 grams of which 93% was 4-nitro-2'-methoxydiphenyl ether. 5

Example 7

4-nitrodiphenyl sulphide

10 4-Nitrodiphenyl sulphide was produced by the method used in Example 5 but using 110 grams thiophenol instead of the 2,5-dichlorophenol. 10

Example 8

4-nitro-2'-hydroxydiphenyl ether

15 110 grams catechol and 1000 ml toluene were placed in a flask equipped with a dropping funnel, Dean and Stark apparatus and a gas inlet tube. The mixture was stirred and the air replaced by nitrogen. A solution of 40 grams sodium hydroxide in 60 grams water was added and the water removed by azeotropic distillation. The reaction was then continued as in Example 5 except that a nitrogen atmosphere was maintained until completion of the reaction. 15

20 The yield was 230 grams of 94% pure 4-nitro-2'-hydroxydiphenyl ether. 20

Example 9

4-methyl-4'-nitrodiphenyl sulphide

25 73.5 grams 4-methyl-thiophenol were, as described in Example 1, converted to the sodium salt using 23.7 grams sodium hydroxide. 25

30 Then a solution of 93.3 grams 4-nitrochlorobenzene in 600 ml N,N-dimethylformamide was added slowly whilst fractionating off the residual toluene. The addition was complete in one hour. After removal of the toluene, reflux was continued for 2 hours, the solution being then cooled and the salt removed by filtration. The solvent was recovered by the use of a rotary evaporator and the residue was recrystallised from 400 ml methylated spirits. 125 grams of solid 4-methyl-4'-nitrodiphenyl sulphide crystallised out and a further 12 grams was found in the mother liquors mixed with p-chloronitrobenzene. 30

Example 10

4-nitro-diphenyl ether

35 0.5 mole phenol was converted to its anhydrous sodium salt in the same manner as 4-chlorophenol in Example 1 and the major part of the toluene was removed by distillation. 300 ml dimethylformamide were added and the residual toluene was fractionated off at reduced pressure. A mixture of 0.49 mole 4-nitrobenzonitrile and 150 ml dimethylformamide were added and the whole reaction mixture was held at 40 120—125°C for 4½ hours. Approximately 300 ml dimethylformamide were distilled off under reduced pressure and the residue was poured into cold water. 0.41 moles of the required ether, 4-nitrodiphenyl ether, was found in the solid material obtained. 40

45 0.39 mole of the ether was recovered by vacuum distillation. In the Examples the dimethylformamide was recovered by conventional fractionation methods and recovery was in excess of 90%. 45

The compounds 2,4'-dinitrodiphenyl ether and 2,4,5-trichloro-4'-nitrodiphenyl ether, have been prepared in an analogous manner.

50 In a further Example, the 4-chloro-nitrobenzene used in Example 1 was replaced by 1 mole of 4-nitrobenzonitrile. The yield of 4-nitro-4'-chlorodiphenyl ether was about 75%. 50

WHAT WE CLAIM IS:—

55 1. A process for the production of a diaryl ether, which comprises reacting sodium phenoxide ArONa with an aryl compound Ar'X in a polar organic solvent, in which Ar and Ar' are aryl groups, and X is a nuclear, replaceable halogen or pseudohalogen. 55

2. A process for the production of a diaryl sulphide, which comprises reacting a sodium aryl sulphide ArSNa with an aryl compound Ar'X in a polar organic solvent, in which Ar and Ar' are aryl groups, and X is a nuclear, replaceable halogen or pseudohalogen.

3. A process according to claim 1 or claim 2, in which the reaction is carried out at a temperature not below 80°C.
4. A process according to claim 1 or claim 2, in which the reaction is carried out at a temperature in the range 80—100°C.
5. A process according to claim 4, in which the reaction mixture is subsequently held at a temperature above 100°C for a time sufficient to render the precipitated sodium salt more amenable to filtration.
6. A process according to claim 1 or claim 2, in which the reaction is carried out at a temperature in the range 100—130°C.
7. A process according to claim 2, in which the reaction is carried out at a temperature in the range 140—200°C.
8. A process according to claim 2, in which the reaction is carried out under reflux.
9. A process according to any one of the preceding claims, in which the solvent is an N-alkylated alkanolic acid amide.
10. A process according to claim 9, in which the solvent is dimethylformamide.
11. A process according to any one of the preceding claims, in which X is chlorine.
12. A process according to any one of the preceding claims, in which the compound Ar'X contains an electron-withdrawing group as a further nuclear substituent.
13. A process according to claim 12, in which the electron-withdrawing group is ortho or para to the substituent X.
14. A process according to claim 12 or claim 13, in which the electron-withdrawing group is a nitro group.
15. A process according to any one of the preceding claims, in which the phenoxide ArONa or sulphide ArSNa is produced in situ.
16. A process according to claim 15, in which the phenoxide or sulphide is formed from the phenol or thiophenol and concentrated aqueous sodium hydroxide in a liquid medium which forms an azeotrope with water.
17. A process according to claim 16, in which water formed in the reaction and water introduced with the sodium hydroxide is removed as an azeotrope with the liquid medium.
18. A process according to any one of the preceding claims, in which the group Ar of the phenoxide or sulphide contains an electron-withdrawing group in the 2, 4 or 6 position.
19. A process according to claim 18, in which said group is a nitro group.
20. A process according to any one of claims 1 to 18, in which the compound ArONa or ArSNa contains NO₂ or Cl in the 4-position.
21. A process according to any one of claims 1 to 18, in which the sodium compound is the 2,5-dichloro- or the 2,4,6-trichlorophenoxide or the thio analogue of either phenoxide.
22. A process according to any one of claims 1 to 18, in which the sodium compound contains a methoxy or hydroxy group in the 2-position.
23. A process according to any one of claims 1 to 18, in which the sodium compound contains an alkyl group in the 4-position.
24. A process for the production of a diaryl ether, substantially as hereinbefore described in Example 1 or Example 2.
25. A process for the production of a diaryl ether, substantially as hereinbefore described in any one of Examples 3 to 6, 8 and 10.
26. A process for the production of a diaryl sulphide, substantially as hereinbefore described in Example 7 or Example 9.
27. A diaryl ether or diaryl sulphide whenever obtained by the process claimed in any one of the preceding claims.

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